Maximising the potential of HPV vaccines

Luttjeboer, Jos; Wondimu, Abrham; Van der Schans, Jurjen; Postma, Maarten J.

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In *The Lancet Global Health*, Kaja M Abbas and colleagues[1] present revised estimates of the worldwide impact of human papillomavirus (HPV) vaccination on prevention of cervical cancer, using the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model. Their updated analysis uses population demography data from the UN World Population Prospects 2019 revision, disability weights from the Global Burden of Disease 2017 study, and cervical cancer burden from the Global Cancer Incidence, Mortality and Prevalence 2018 database.[2–4] The revised estimates suggest that the potential health impact of HPV vaccines is higher than was previously forecast, with health benefits increased to 15–19 cases, 12–14 deaths, and 243–306 disability-adjusted life-years averted per 1000 vaccinated 9-year-old girls, with the upper and lower limits reflecting the estimates for the nonavalent vaccine and bivalent or quadrivalent vaccine, respectively.[5,6] These increased health benefits are assumed to result in improved cost-effectiveness of the vaccines—ie, the costs per fully immunised girl remain similar, while at the same time more cases are averted. The WHO African region is estimated to benefit the most from HPV vaccination introduction and scale-up. However, this will be a challenge in the present situation of HPV vaccine scarcity.[7] In the context of the report by Abbas and colleagues, three issues warrant further consideration: potential differences between the vaccines, potential reduced vaccination schedules, and prevention of cancers other than cervical cancer.

In this study, Abbas and colleagues assume equal effectiveness of the bivalent and quadrivalent vaccine in targeting two oncogenic types, HPV 16 and 18.[1] Although this assumption holds when considering the effectiveness of both vaccines against HPV 16 and 18, a substantial difference in effectiveness against cervical intraepithelial neoplasia grade 3 (CIN3+) lesions, irrespective of HPV type, has been noted previously. Randomised controlled trials have shown that in baseline HPV-negative cohorts, the effectiveness against CIN3+, irrespective of HPV type, was 93% for the bivalent vaccine and 43% for the quadrivalent vaccine.[8] This trend is also seen in girls routinely vaccinated against HPV in Scotland (89% effectivness against CIN3+, bivalent vaccine) and Sweden (64%, quadrivalent vaccine).[9,10] Therefore, the impact of the bivalent vaccine might exceed the benefits estimated by Abbas and colleagues.[1] However, the effectiveness of all HPV vaccines is based on surrogate outcomes for cervical cancer, because follow-up to assess the vaccines' impact on cervical cancer would span over decades. Over time, we will learn how these surrogate outcomes relate to cervical cancer and if there are differences between the bivalent and quadrivalent vaccine.

In a meeting in October, 2019, the WHO Strategic Advisory Group of Experts on Immunization noted the shortage of HPV vaccines. The group advised potentially pausing implementation of extended vaccination strategies for older girls or women and boys, and applauded the ongoing research on single-dose effectiveness.[11] Pragmatic analyses of data in two clinical trials in which planned doses were missed, as well as evaluations in real-world contexts, have shown the effectiveness of one-dose schedules. In a white paper published by the Single-Dose HPV Vaccine Evaluation Consortium (led by PATH), 23 studies are identified in a systematic review, most of which found the highest effectiveness with three doses, followed by two doses, and then one dose.[12] Of note, the more recent studies with younger vaccines showed small or no differences by the number of doses. A single-dose strategy would help to alleviate the issues concerning shortages of HPV vaccine, and would enhance the potential to introduce and scale up vaccination in regions where the burden of cervical cancer is highest. Although the evidence for the effectiveness of single-dose vaccination is not yet as clear as for two or three doses, we could consider taking a leap of faith, as was done with the surrogate cervical cancer outcomes, to increase the potential of HPV vaccines by switching to a single-dose strategy.

This study, and much of the debate around HPV vaccination, focuses on cervical cancer. However, HPV is known to infect other areas in the anogenital tract, including the vagina, vulva, penis, and anus, and also areas in the head and neck.[8] Globally, the annual incidence of non-cervical HPV-related cancers is estimated to be 113 000 in both sexes.[13] Averting these infections and associated cancers by vaccination will potentially improve the cost-effectiveness of the vaccine, and could even make it cost-saving. Including

these non-cervical HPV-related cancers in cost-effectiveness analyses of HPV vaccines could add an additional incentive for introducing HPV vaccination.

JL works part-time for Asc Academics, a consultancy with various pharmaceutical companies among its clients, including two companies (Merck Sharp & Dohme and GlaxoSmithKline) that are developing, producing, and marketing HPV vaccines. MJP reports grants and personal fees from Merck Sharp & Dohme, GlaxoSmithKline, Pfizer, Boehringer Ingelheim, Novavax, Bristol-Myers Squibb, AstraZeneca, Sanofi, IQVIA, and Seqirus; personal fees from Quintiles, Novartis, and Pharmerit; grants from Bayer, BioMerieux, WHO, the EU, the FIND project, Antilope, DIKTI, LPDP, and Budi; acts as an advisor to Asc Academics; and holds stocks in Ingress Health and PAG. AW and JVdS declare no competing interests.

*Jos Luttjeboer, Abrham Wondimu, Jurjen Van der Schans, *Maarten J Postma*
m.j.postma@rug.nl

Department of Medical Microbiology (JL) and Department of Health Sciences (AW, JVdS), University Medical Center Groningen, Department of Economics, Econometrics and Finance, Faculty of Economics & Business (JVdS, MJP), and Unit of PharmacoTherapy, Epidemiology and Economics, Department of Pharmacy (MJP), University of Groningen, Groningen 9713 AV, Netherlands; Department of Pharmaceutics, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia (AW); and Department of Pharmacology and Therapy, Airlangga University, Surabaya, Indonesia (MJP)

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